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# Respiratory Responses in Humans Repeatedly Exposed to Low Concentrations of Ozone 1-3

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16. ABSTRACT

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# Respiratory Responses in Humans Repeatedly Exposed to Low Concentrations of Ozone[1-3]

L. J. FOLINSBEE, J. F. BEDI, and S. M. HORVATH

**SUMMARY**

The effect of repeated daily exposure to a low concentration of ozone was studied in healthy adult males to answer 2 questions: (*1*) Is there a cumulative effect of exposure to ozone from day to day, causing an exacerbation of changes in pulmonary function? (*2*) Does the subject develop resistance or adaptation to the respiratory effects of ozone? The subjects were exposed for 2 h in an environmental chamber at 35 °C and 45 % relative humidity to filtered air on day 1, to ozone on days 2 through 4, and to filtered air on day 5. Three groups of subjects were used, each exposed to a different concentration of ozone: group 1 (n = 10), 0.20 ppm of ozone; group 2 (n = 10), 0.35 ppm of ozone; group 3 (n = 8), 0.50 ppm of ozone. There were no acute or cumulative effects of repeated exposure to 0.20 ppm of ozone. With exposure to 0.35 ppm of ozone, there were decrements in forced expiratory parameters on day 2. These changes were greater on day 3, but were largely absent on days 4 and 5. In group 3, there were marked effects of ozone on pulmonary function on day 2, but these changes were greatest on day 3. Significant effects (although of lesser magnitude) were also observed on day 4. The forced expiratory volume in 1 s decreased 8.7 % on day 2, 16.5 % on day 3, and 3.6 % on day 4. The subjects claimed the most discomfort on day 3; many noted marked improvements on day 4, the third consecutive day of exposure to ozone. Two additional subjects were exposed to 0.50 ppm of ozone for 4 consecutive days. Although effects of ozone on pulmonary function were observed on the first 2 days of exposure, few effects were seen on the third day, and no effect was observed on the fourth day. We conclude that there is some short-term cumulative effect of exposure to concentrations of ozone above the threshold for producing acute respiratory effects. This is followed by a period of resistance or adaptation in which there is a marked lessening of the effect of ozone on pulmonary function and on the subjective feelings of discomfort associated with exposure to ozone.

## Introduction

The finding of a decreased sensitivity to ozone in those who reside in polluted areas (1, 2) or who have been repeatedly exposed to ozone (3, 4) has clearly suggested that humans may in some way become adapted to exposure to ozone. Whether or not such adaptation confers any beneficial or protective effects on the lung during subsequent exposure to ozone, it appears that subjective complaints and objective indications of acute impairment of pulmonary function are diminished. However, in addition to a decreased sensitivity to ozone, there seem to be 2 alternative explanations for the apparent adaptation phenomena. A delayed response to the exposure to ozone could explain the lessened or abolished response at the end

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[1] From the Institute of Environmental Stress, University of California, Santa Barbara, Santa Barbara, Ca. 93106.

[2] This work was supported in part by the Environmental Protection Agency. Report by S. M. Horvath, "Adaptation to Ozone," prepared under Contract EPA 68-02-1723.

[3] The nature and purpose of the study and the risks involved were explained verbally and were given on a written form to each subject before his voluntary consent to participate. The protocol and procedures for this study have been approved by the Committee on Activities Involving Human Subjects, of the University of California, Santa Barbara.

of exposure, or an initial response might be reversed during the exposure. Such responses would not be observed by measuring responses only before and after exposure.

We were also interested in the possibility of potentiation of the response to ozone after repeated exposures to ozone, which was previously alluded to by Hackney and co-workers (3, 5) but was not examined in more recent reports. Could low concentrations (0.20 to 0.35 ppm) of ozone, which produce few, if any, symptoms after an initial 2-h exposure, cause significant pulmonary changes on subsequent exposures?

Accordingly, we examined the respiratory responses in 3 groups of subjects exposed repeatedly to low concentrations of ozone: 0.20, 0.35, and 0.50 ppm of ozone. These concentrations are equivalent to first-, second-, and third-stage "alert" levels in California.

## Methods

*Subjects*. Thirty men 18 to 29 yr of age served as subjects in this experiment. Physical data for these subjects are summarized in table 1. The purpose of the experiment was explained to the subjects, and each gave his informed consent. Each subject was medically screened. A medical history questionnaire, a resting 12-lead electrocardiogram (ECG), a battery of clinical spirometric tests, a submaximal exercise test including ECG, and a physical examination were used in evaluating each subject.

One half of these subjects (15 of 30) had lived in or grown up in areas considered to have significant levels of photochemical air pollution, although none had done so immediately before the study. Twenty subjects reported having experienced some subjective discomfort, mainly eye irritation, during previous exposures to ambient air pollution; only 9 subjects reported previous difficulty with breathing, such as shortness of breath or chest tightness. Seven subjects had a history of some allergy; 3 reported having had "asthma" as a child. Ten subjects were former smokers; none had smoked heavily (never more than 1 pack/day), and none had smoked within the year before the study.

*Experimental design*. The subjects were randomly assigned to one of 3 groups (10 subjects/group) designated groups 1, 2, and 3. The nominal ozone concentrations selected were 0.20, 0.35, and 0 50 ppm for groups 1, 2, and 3, respectively. Each subject was exposed for 2 h on each of 5 days. In order, the exposure conditions were as follows: filtered air on day 1; ozone on days 2 through 4; filtered air on day 5. During the exposure, the subjects exercised on a treadmill at a load sufficient to produce a ventilatory volume of approximately 30 L/min. Ambient conditions were 35° C and 45 % relative humidity, because smog "alerts" are commonly accompanied by hot, dry weather.

*Protocol*. On arrival at the laboratory, the subject weighed himself, inserted a rectal temperature probe, and was examined by a physician. Electrocardiograph chest leads were then attached. Pulmonary function tests were performed, including forced vital capacity (FVC), functional residual capacity (FRC), and maximal voluntary ventilation (MVV). On completion of these tests, the subject entered the environmental chamber already set for the appropriate conditions.

During the 2-h exposure, the subject exercised for 15 min each half hour, with a 15-min rest period after each exercise period. During each of the exercise periods, ventilation, respiratory frequency, and cardiac frequency were determined. The FVC test was performed (3 repetitions) during the intervening rest periods. At the completion of the exposure, the subject left the chamber, was re-examined by a physician, and repeated the pre-exposure pulmonary function tests. The subject also completed a written questionnaire and was verbally interviewed regarding the symptoms he might have experienced in the chamber.

On many occasions, 2 subjects were present in the chamber at the same time. In such cases, the starting times of the 2 subjects were staggered by 45 min so that

TABLE 1

PHYSICAL CHARACTERISTICS OF SUBJECTS

| Subjects | Age (*yr*) | Height (*cm*) | Weight (*kg*) | FVC (*ml*) | FVC (% *pred.*) | $FEV_1$/FVC (%) |
|---|---|---|---|---|---|---|
| Group 1 | | | | | | |
| $\bar{X}$ | 22.7 | 181.2 | 72.7 | 6058 | 107.6 | 81.3 |
| Range | 18-28 | 170-196 | 56-93 | 4,961-7,276 | 91-124 | 73-88 |
| Group 2 | | | | | | |
| $\bar{X}$ | 21.4 | 179.8 | 75.0 | 5864 | 105.0 | 82.7 |
| Range | 18-29 | 172-189 | 63-87 | 5,130-7,041 | 97-118 | 74-90 |
| Group 3 | | | | | | |
| $\bar{X}$ | 21.3 | 178.1 | 70.6 | 5860 | 107.2 | 81.9 |
| Range | 19-26 | 168-188 | 53-83 | 4,998-6,961 | 88-123 | 68-90 |

*Definitions of abbreviations*: FVC = forced vital capacity; % pred. = percentage of the value predicted according to the data of Anderson and co-workers (6); $FEV_1$/FVC = forced expiratory volume in 1 s, expressed as a percentage of the FVC; $\bar{X}$ = mean.

they could alternate on the treadmill and so that the measurements before and after exposure would not overlap.

*Measurements*. Pulmonary function tests were performed with the subject standing. A 13.5-L Benedict-Roth spirometer was used for the determination of the lung volumes, vital capacity (VC), inspiratory capacity (IC), and expiratory reserve volume; the forced expiratory parameters, FVC, forced expiratory volume in 1 s ($FEV_1$), forced expiratory volume in 2 s ($FEV_2$), forced expiratory volume in 3 s ($FEV_3$), forced expiratory flow after exhalation of 50 % of the FVC ($FEF_{50\%}$), forced expiratory flow after exhalation of 75 % of the FVC ($FEF_{75\%}$), forced expiratory flow during the middle half of the FVC ($FEF_{25-75\%}$); and MVV (7). The FRC was determined by a helium-dilution technique. All flows and volumes were corrected to BTPS. The spirometer was interfaced with a PDP-12 laboratory computer, which provided on-line analysis of the pulmonary function tests. Ventilation volume was determined by having the subject breathe through a low-resistance breathing valve into a chain-compensated 120-L spirometer. Respiratory frequency was determined from a continuous recording of expired $CO_2$ concentration. Cardiac frequency was determined from the electrocardiogram (reciprocal of the mean R-R interval for 6 beats).

A double-walled acrylic environmental chamber, 1.8 m wide by 2.4 m long by 2.6 m high, was used for exposures. Inlet air was dried (Drierite, silica gel) and passed through activated charcoal and particulate filters at 0.5 $m^3$/min; chamber air turnover time was 22 min.

A dehumidifier and steam inlet were used to maintain relative humidity at 45 %, and an electric heater and air conditioner were used to maintain temperature at 35 °C. Ozone was generated from 100 % $O_2$ using an ultraviolet ozone generator (Ozone Research Inc.) or a corona discharge ozone generator (8). The concentration of ozone was monitored continuously using a chemiluminescent ozone meter (McMillan). The monitor was calibrated with a factory-calibrated ozone generator (Monitor Labs) that was checked periodically against the neutral buffered-potassium iodide (KI) method (9). It has been demonstrated recently that neutral buffered-KI methods yield results as much as 20 % higher than those determined by ultraviolet spectrometry (10). We have not attempted to correct our values, because the specific method we used was not used in the comparisons described. (As an approximation, the nominal concentrations 0.20, 0.35, and 0.50 ppm of ozone may be more nearly 0.20, 0.32, and 0.43 ppm of ozone). The average chamber ozone concentrations (ppm) for the 3 groups on each of the 3 days of exposure to ozone are as follows: group 1, 0.20, 0.18, 0.20 (± 0.02); group 2, 0.34, 0.35, 0.34 (± 0.03); group 3, 0.46, 0.48, 0.48 (± 0.07).

*Analysis of data*. Data were treated by a 3-factor analysis of variance with repeated measures across days and exposure time. Treatment conditions were (*1*) subject group (ozone concentration); (*2*) day of exposure; (*3*) time period during exposure (before and after test or time intervals within the exposure). When interactions were significant, a test for simple main effects was applied, followed by a Newman-Keuls test of ordered means when appropriate. All hypotheses were tested for significance at the 0.05 level of confidence; any reference to "difference," "significant," "decreased", and so on refers to this level of significance unless specifically stated otherwise.

## Results

The results of the pulmonary function test performed before and after the exposure are summarized in figure 1A-C (a complete listing of the data is available in an Environmental Protection Agency report.[2]) There were no differences between the pulmonary function measurements obtained before exposure on days 1 through 5 at any concentration of ozone. There was only one difference between groups that was significant: the $FEV_1$ after exposure to 0.35 and 0.50 ppm of ozone on day 3 (i.e., second day of exposure to ozone) was less than that after exposure to 0.20 ppm of ozone.

There were no effects of exposure to 0.20 ppm of ozone on any of the 3 days of exposure.

After exposure to 0.35 ppm of ozone, $FEV_1$ and $FEF_{25-75\%}$ were decreased on day 2 (first day of exposure to ozone). The FVC, $FEV_1$, and $FEF_{25-75\%}$ were significantly decreased on day 3 (second day of exposure to ozone). No changes in pulmonary function occurred on days 1 or 5. The largest decrement in pulmonary function generally occurred on the second day of exposure to ozone (day 3), but these changes were not significantly larger than those seen on the first and third days of exposure to ozone (days 2 and 4).

In the third subject group, exposed to 0.50 ppm of ozone, the most dramatic changes were seen. The FVC, $FEV_1$, and $FEF_{25-75\%}$ all decreased after exposure to ozone on days 2 and 3. The $FEV_1$ and $FEF_{25-75\%}$ were also decreased on day 4, the third day of exposure to ozone. The decreases in FVC, $FEV_1$, and $FEF_{25-75\%}$ were significantly greater on day 3 (the second day of exposure to ozone) than on either day 2 or day 4. A decrease in IC usually accompanied a decrease of FVC, but the data are not presented here.[2]

Two additional subjects were exposed for 4 consecutive days to 0.50 ppm of ozone. The changes seen in FVC and $FEV_1$ during this period are shown in figure 2. They showed a somewhat different response than was observed for group 3. The effect of ozone was greatest on the first day of exposure and became progressively less on consecutive days, such that no effects were seen on the third and fourth days of exposure. Only 1 of 8 subjects in group 3 showed a lesser response on

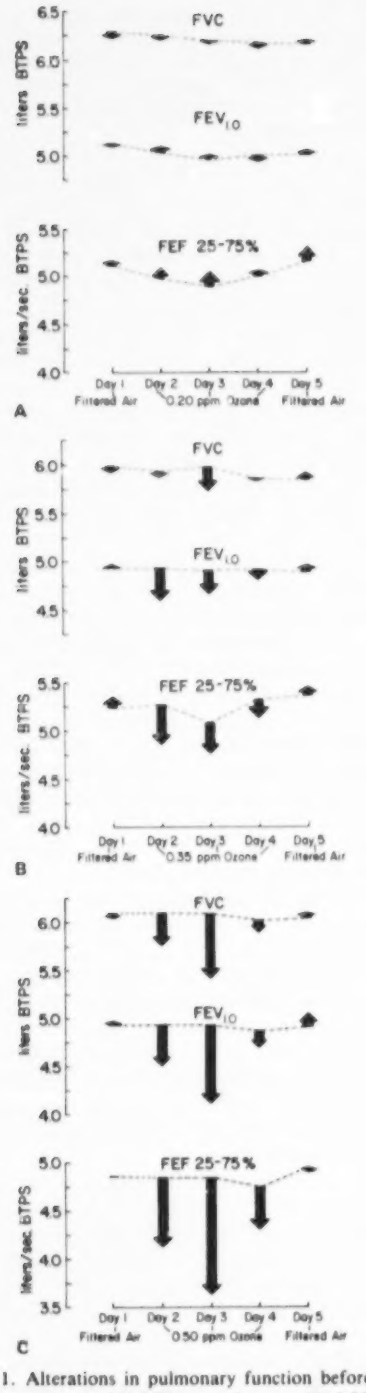


Fig. 1. Alterations in pulmonary function before and after exposure to (*A*) 0.20 ppm of ozone, (*B*) 0.35 ppm of ozone; and (*C*) 0.50 ppm of ozone for 2 h on each of 3 consecutive days. These exposures were preceded and followed by a control exposure to filtered air. The dashed line represents the day-to-day variance in the value before exposure, and the tip of the arrow represents the value after exposure. FVC = forced vital capacity; $FEV_{1.0}$ = forced expiratory volume in 1 s; $FEF_{25-75\%}$ = forced expiratory flow during the middle half of the FVC.

the second day of exposure to ozone than on the first.

The pulmonary function variables were also analyzed across periods of time during the exposure, including the measurements before and after exposure. The measurements taken during exposure were made near the end of each 30-min period.

Briefly, no significant effects were observed during any period in group 1 (exposure to 0.20 ppm of ozone) with the exception of some random changes in $FEF_{25-75\%}$ that occurred on day 1 and day 4.

In the group exposed to 0.35 ppm of ozone, significant changes in pulmonary function (FVC, $FEV_1$, $FEV_3$, and $FEF_{25-75\%}$) were confined to those seen at the end of exposure, i.e., at the last measurement made within the chamber (at approximately 115 min of exposure), and at the tests after the exposure. The VC and expiratory flows were significantly lower at this time than when measured before exposure or within the first hour of exposure (see figure 3A for $FEV_1$).

In the group exposed to 0.50 ppm of ozone, significant decreases in FVC and $FEV_1$ occurred within the first hour of exposure on the first and second days of exposure to ozone. The $FEF_{25-75\%}$, although not decreased during the first hour on the first day of exposure to ozone, was significantly decreased during the first hour on the second day of exposure to ozone. In most cases, the change measured at the end of exposure while the subject was still in the chamber showed the greatest decrement in function. The decreases in the measured parameters at the end of exposure were smaller on the third day of exposure to ozone, but the changes were still significant. However, no significant change in pulmonary function occurred within the first hour of exposure on this third day of exposure. The $FEV_1$ data are presented graphically in figure 3B.

Analysis of the pulmonary function data across day of exposure revealed that in group 3 (exposed to 0.50 ppm of ozone), the effects of exposure to ozone were greatest on day 3. These differences were significant after approximately 50 min of exposure up to and including the period after exposure. The parameters that demonstrated the most

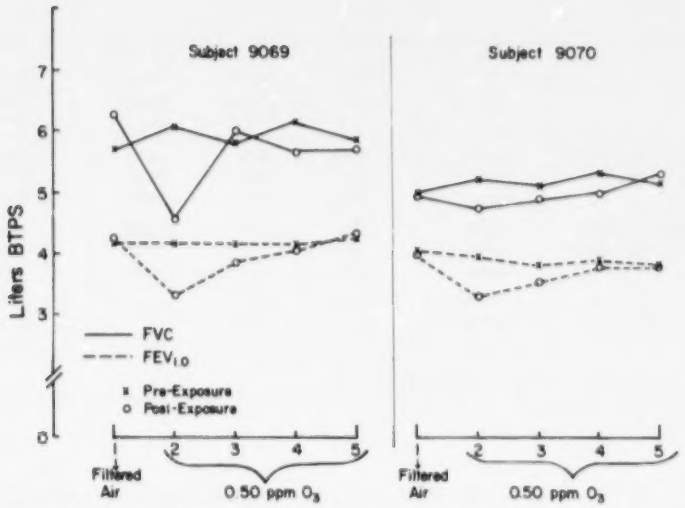


Fig. 2. Forced vital capacity (FVC) and forced expiratory volume in 1 s ($FEV_1$) in 2 subjects exposed for 4 days to 0.50 ppm of ozone ($O_3$).

clear-cut differences across days were FVC, $FEV_1$, and $FEF_{25-75\%}$.

In Group 2 (exposed to 0.35 ppm of ozone), the greatest decrement in pulmonary function also occurred on day 3 (i.e., second day of exposure to ozone).

There were no significant changes in the respiratory pattern that could be attributed to exposure to ozone (11). The lack of a change here could have been due to the concurrent exposure to heat, although we have not previously found tachypnea and decreased tidal volume at this low workload (11). Changes in ventilation and heart rate are not reported here, but are included in a report to the EPA.[2]

*Symptomatology*. The subjects were asked a series of questions at the end of each exposure period to determine their subjective impression of the exposure. One question, which gives an over-all view, was "How would you compare this exposure with the previous exposure day: worse, better, or the same?" Their responses are summarized in table 2. Group 1 (exposed to 0.20 ppm of ozone) showed no consistent pattern of responses. Group 2 (exposed to 0.35 ppm of ozone) generally agreed that the first day of exposure to ozone was worse than the day of exposure to filtered air, but there was little consensus on comparisons of other days. Group 3 (exposed to 0.50 ppm of ozone) unanimously agreed that the first day of exposure to ozone (day 2) was worse than the exposure to filtered air, and most believed that the second day of exposure to ozone was worse than the first. However, they unanimously agreed that the third day of exposure to ozone was better than the second, and most believed that the final day of exposure to filtered air was better than the third day of exposure to ozone.

Symptoms experienced during exposure were reported by the subjects in the interview after the exposure. Mild nausea was experienced by a few subjects, but this occurred mainly on the first and second day of exposure to ozone in group 3. The incidence of cough and shortness of breath was also greatest on the first and second days of exposure to ozone. These symptoms were related to exposure to ozone, and it is interesting that such symptoms were reported less frequently on the third day of exposure to ozone, when the objective measures of pulmonary function showed less impairment. Other symptoms such as dizziness and headache were probably related to the associated exposure to heat (35° C, 45 % relative humidity), which occurred on all days, because these symptoms were not related to the exposures to ozone.

## Discussion

The possible mechanisms for alteration in pulmonary function after exposure to ozone have been discussed previously (3, 11–13). The changes in flow and volume measurements observed in these subjects compare favorably with the results reported by others (1, 5, 14) and with those seen

TABLE 2

SUBJECTIVE COMPARISONS OF EXPOSURE DAYS* RELATIVE TO PRECEDING DAY

| | | Day 2 Versus Day 1 | Day 3 Versus Day 2 | Day 4 Versus Day 3 | Day 5 Versus Day 4 |
|---|---|---|---|---|---|
| Group 1 (n = 10) | Worse† | 30% | 50% | 40% | 10% |
| $[O_3]$‡ = 0.20 ppm | Same | 30% | 30% | 20% | 50% |
| | Better | 40% | 20% | 40% | 40% |
| Group 2 (n = 10) | Worse | 70% | 30% | 30% | 30% |
| $[O_3]$ = 0.35 ppm | Same | 10% | 20% | 10% | 20% |
| | Better | 20% | 50% | 60% | 50% |
| Group 3 (n = 8) | Worse | 100% | 62% | - - - | - - - |
| $[O_3]$ = 0.50 ppm | Same | - - - | 13% | - - - | 13% |
| | Better | - - - | 25% | 100% | 87% |

* Day 1 and day 5, filtered air; days 2 through 4, ozone.

† Entries in this column indicate that day 2 was subjectively worse than day 1, or day 3 was worse than day 2, and so on.

‡ $[O_3]$ = concentration of ozone.

previously in a study in which we examined the dose-response relationship to ozone (11).

One of the aims of the present study was to determine whether exposure to low concentrations of ozone, which normally produce no effects on pulmonary function, would cause alterations if the subject were exposed on successive days. The results of the studies with group 1 (exposed to 0.20 ppm of ozone, which has not been shown to produce acute changes in pulmonary function) (11) demonstrated that no measurable effects occurred after 3 consecutive days of daily 2-h exposures. This not only shows that at this concentration of ozone there is no short-term cumulative effect of exposure to 0.20 ppm of ozone on pulmonary function, but also eliminates the possibility that the observed responses could have been due to psychologic factors related to perception of ozone odor. With Groups 2 and 3 (exposed to 0.35 and 0.50 ppm of ozone), the decreases in several of the parameters were greater on the second day of exposure to ozone than on the first day. Similar observations were made by Hackney and co-workers (3) on a smaller group of subjects (n = 6) exposed repeatedly to 0.50 ppm of ozone and by Farrell and associates (4) in a group of 14 subjects exposed to 0.4 ppm of ozone for 5 days. Farrell and coworkers (4) observed significant decreases in $FEV_1$ for as long as 4 days of exposure to ozone, although the greatest decrease still occurred on the second day. Because this pattern of a greater decrement on day 2 of exposure to ozone was seen in several of the measured parameters, it appears that there may be some enhancement of sensitivity from the initial exposure, although there were changes in baseline measurements across the 3 exposure days. Because the mechanism for the initial changes in pulmonary function is not entirely clear, the explanation for the apparent increased sensitivity to ozone on the second day of exposure must necessarily be speculative.

One conclusion we could tentatively draw from these observations is that, for subthreshold concentrations of ozone, potentiation of the ozone effect does not occur with consecutive exposures; but with concentrations above threshold, there is an apparent potentiation of the ozone effect. This may result from an increased sensitivity of the irritant receptors, which are believed to be partially responsible for some alterations in pulmonary function consequent to the exposure to ozone.

Lee and associates (15) demonstrated hyperreactivity to inhaled histamine in dogs 1 and 5 days after a 2-hour exposure to 1 ppm of ozone. However, the dogs were not hyperreactive immediately after the exposure. The response was abolished by vagal cooling and by pretreatment with atropine, indicating that vagal cholinergic pathways were involved. One possible mechanism is that airway receptors are sensitized by damage to the airway epithelium. In man, this hypersensitivity was present immediately after exposure, but was present in only 4 of 8 subjects by 24 h after exposure (16). However, as Hackney and associates (3) suggested, some of the effects of ozone could be produced in the peripheral airways, where neither irritant receptors nor vagal efferents would be involved. The mechanism of a residual effect at this level is unknown and could not be assessed from the tests used in the present study. Alterations in the characteristics of surfactant or mucous glycoproteins may contribute to such responses. Last and associates (17) have demonstrated a transient decrease in glycoprotein secretion *in vitro* followed by in-

creased glycoprotein secretion in tracheal cells repeatedly exposed to ozone. The response took approximately 1 wk to occur, but because this was an *in vitro* study, the time course of the response might not be strictly comparable to the *in vivo* response of humans or animals exposed to ozone. If such a response occurred in man, it could partially explain the initial increased sensitivity to ozone as a result of decreased quantity of protective mucus lining the airways. The subsequent lessened sensitivity to ozone could result from increased protection accorded by production of more mucus.

We also proposed to examine whether the rate of change in the pulmonary function parameters varied from day to day with repeated exposure to ozone. The time course of response has been examined previously (14, 18), although in less detail. The analysis of variance and the graphic representation of the data (figure 3) indicate that the changes in pulmonary function occurred earlier on the second day of exposure to ozone than on the first and that the magnitude of the change was generally greater at any given time on the second day of exposure to ozone than on the first.

An important aspect of this study was to examine whether man developed a tolerance or adaptation to exposure to ozone. Group 2 (exposed to 0.35 ppm of ozone) demonstrated significant decreases in VC and maximal expiratory flow on the first 2 days of exposure to ozone, but showed no

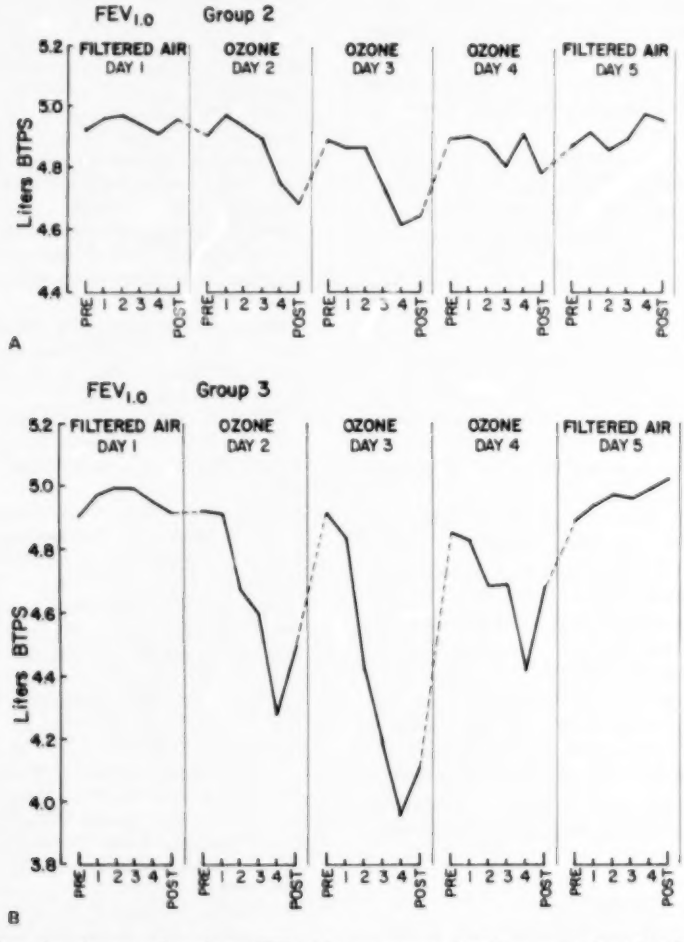


Fig. 3. Forced expiratory volume in 1 s ($FEV_{1.0}$) in two groups of subjects exposed to (A) 0.35 ppm $O_3$, and (B) 0.50 ppm $O_3$ for three successive days. Numbers on the abscissa represent successive half-hour periods.

changes on the third day of exposure. A similar trend was evident for the group 3 subjects (0.50 ppm of ozone), but significant decrements were observed in several parameters on the third day of exposure. Thus, whereas adaptation or tolerance appeared to be more or less complete within 3 days for the group exposed to 0.35 ppm of ozone, the subjects exposed to 0.50 ppm of ozone had not become fully adapted within 3 days. This agrees with observations of Farrell and coworkers (4). The data of Hackney and associates (2) suggests that their subjects had become adapted by the third day and most certainly by the fourth day of exposure to ozone. To confirm that adaptation would have been complete with additional exposures, 2 additional subjects in the present study were exposed to 0.50 ppm of ozone for 4 consecutive days; they had clearly become adapted by the fourth day of exposure. Additional studies (unpublished observations) in 15 subjects exposed for 5 consecutive days to 0.50 ppm of ozone support this observation.

Tolerance to the acute lethal effect of exposure to ozone in animals (19) is related to the development of pulmonary edema and may be conferred by other edemagenic agents (20). It appears that this is not the same phenomenon that we are observing in humans. The observations of Last and associates (17) on alterations in glycoprotein secretion offer a more likely mechanism for this adaptation. Tolerance in animals is mainly tissue specific, i.e., only exposed lungs appear to become tolerant (21). Recent evidence suggests there may also be a small systemic component to tolerance (22). Whether or not this is true in humans remains to be demonstrated.

In previous studies of exposure of humans to ozone (5, 12, 14), subjective complaints of cough, chest tightness, headache, and so on have generally paralleled the alterations in the objective measures of pulmonary function, an observation supported by the present study. It appears that the mechanisms responsible for the production of the subjective sensations experienced by these subjects have some relationship, at least in time, to the mechanisms responsible for the alterations in pulmonary function. In addition, adaptation to the effects of ozone on pulmonary function also coincides with a decrease in subjective discomfort.

*Acknowledgment*

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